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FEASIBILITY OF A FETAL MEASUREMENT ELECTRODE SYSTEM

Purchase Order T-4777E

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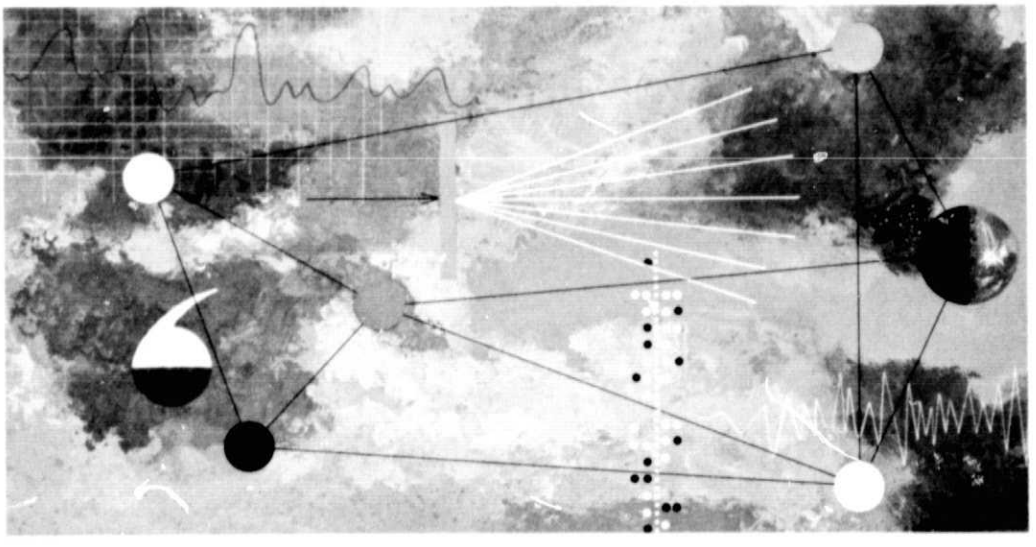

"Measurement is the basis of all knowledge"

Lord Kelvin

FINAL REPORT

Beckman®

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January 1977

Prepared for:

National Aeronautics and Space Administration
Johnson Spacecraft Center
Houston, Texas 77058

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ADVANCED TECHNOLOGY OPERATIONS
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I. INTRODUCTION

This is the final report under Purchase Order T-4777E for studying the feasibility of developing a fetal measurement electrode system.

This report summarizes findings of the study, concludes that all monitoring requirements are not currently satisfied, and presents an approach to provide a multiparametric monitoring system through combinations of existing transducers. This monitoring system would be appropriate, not only for intrapartum monitoring, but also for neonatal and adult blood gas evaluations.

During this study, a literature search was conducted to provide an insight into current state-of-the-art in fetal monitoring. A reference list in this report includes all literature cited in the report, plus many others containing background and supplementary information. A separately-bound volume accompanying this report--Materials Collected During Contract Period--contains reprints of all listed references.

II. CURRENT STATE-OF-THE-ART

The primary purpose of monitoring the fetus during the critical delivery period is to detect evidence of hypoxia, i.e., lack of oxygen to the fetus. Limited oxygen availability to the fetus can cause irreversible brain damage and even death.

As reviewed by Ziehm,[1] auscultation of the fetal heart was begun early in the 19th century. Listening to the fetal heart sounds with the fetal stethoscope was then, and continues to be, an intermittent procedure, usually done between labor contractions.

Initially the relationship of Fetal Heart Rate (FHR) to hypoxia was not well understood, but with the advent of continuous fetal heart rate monitoring--both between and during labor contractions--it has become accepted that hypoxia can cause significant changes in fetal heart rates. Spurett[2] reports that in the early 1960's Hon and Caldeyro-Barcia investigated FHR monitoring by direct connection of an electrode to the fetal scalp. This work led to the concept of simultaneous intrauterine pressure recording (IUP) and fetal beat-by-beat analysis and recording of FHR and IUP on a two-channel recorder at a relatively slow chart speed.

This direct approach is relatively artifact-free, although its application is delayed until the amnion is ruptured and fetal presenting-part of a size suitable for electrode attachment is available. Indirect approaches--using microphones, ultrasonic transducers, and abdominal pressure transducers--although applicable in early stages of labor, are artifact prone and consequently less dependable.

Experience with the FHR-IUP patterns lead to fairly clear categorization of FHR patterns with ominous indications. Persistant tachycardia, recurrent deceleration patterns, or limited beat-to-beat irregularity lasting 20 minutes or more, are examples of major signs which may indicate a fetus in danger.[2] Inservice hospital training has brought physician and nurse skills to a level where FHR patterns are now well understood and are employed to manage the patient during delivery.

Because FHR is only an indirect indicator of hypoxia, other methods of analzing fetal well-being were investigated. In 1962, Saling described a method of sampling blood from the presenting fetal part, which is the scalp about 95% of the time.[2] Fetal scalp blood sampling (FSB) is an intermittent procedure; but, as employed in today's obstetric environment, the frequency of and the precise instant for sampling is guided by the FHR and/or IUP patterns. It is well established that an acidotic state, indicated by pH analysis of the FSB, indicates hypoxia of the fetus.[3] It has been shown that maternal acid-base shifts may be reflected into the fetus due to ion transfer across the placenta.[4] Because of

this possible confusion as to the cause of fetal acid-base shift, maternal blood gas analysis concomitant with FSB analysis is recommended.

The addition of periodic FSB pH sampling to the continuous FHR-IUP monitoring reduced the false negative indications to an acceptable minimum; i.e., although the FHR patterns may appear ominous at times, a normal (>7.25 pH) FSB pH taken frequently is indicative of an acceptable Apgar score.[3,4]

Remaining unresolved is the situation where FHR patterns and FSB pH are normal but an infant with low Apgar score is born. In this case, the delivery team is lulled into a false sense of security, and delays delivery (often by C-section) until a damaged infant results.

There remains in fetal monitoring today the need for a more definitive measure of the fetal acid-base balance. This fetal acid-base indicator should be continuous so that a characteristic phasic relationship between maternal contractions, FHR patterns, and fetal acid-base can be learned and used to manage the delivery.

The simultaneous measurement of FHR, P_{O_2}, and P_{CO_2} or pH from the fetal scalp appears to be the ideal solution. The P_{O_2} would indicate the initial transient drop in fetal P_{O_2} during contractions and other manipulations while the pH or P_{CO_2} would indicate the resulting delayed acid-base shift due to significant hypoxic periods.

The benefits of fetal monitoring are not universally accepted, however. The conservative nature of medical practice has perhaps resisted the immediate sweep to fetal monitoring into non-teaching hospitals. Common reasons for resisting the introduction of fetal monitoring are increased Caesarean section rates (C-rates) and additional costs. Another is the statement, "We only have a few *high risk* patients and we can manage them by watching them carefully."

Increase in C-section rates appears to relate to educational level. If the medical personnel have only a cursory knowledge of FHR patterns, and FSB pH

sampling is not practiced, electronic monitoring can indicate an early C-section when unnecessary. However, at Los Angeles County Hospital, where about one-third of all fetuses are monitored, C-section rates have remained stable at about 10%.[1] Although it is true that electronic monitoring increases costs, this fact must be weighed against its potential for preventing deaths and minimizing the number of individuals with birth-caused brain damage who must be maintained in public-supported institutions for life.

According to Quilligan and others there is no such thing as a "low risk" patient.[5] Although populations differ, there is increasing evidence that 100% monitoring is desirable. Quilligan points out that a certain number of "low risk" patients cannot be pre-diagnosed as "high risk" until the fetus is in danger.

Paul, in a paper entitled "Intrapartum Fetal Monitoring: Current Status and the Future,"[6] indicates that the 1970s present a unique opportunity to implement new investigations and techniques to benefit both mother and fetus. He indicates that this is the period for standardization of classification, instrumentation, and data display.

For details, see "Monitoring of the Fetus," by Finster, published in August 1976, in *Anesthesiology*.[7]

III. OXYGEN, CARBON DIOXIDE, AND pH SENSORS

Before describing the latest work on miniature blood gas and pH sensors, it is well to indicate clearly the relationship between continuous FHR and FSB sampling.

The purpose of the FSB pH determination is to reduce the margin of error associated with reference to the FHR patterns alone.[8] Experience has shown that the acid-base status of the infant at birth may in fact be good even though the FHR patterns were abnormal. At this time, the two measurements are complementary--FHR monitoring is used for preliminary screening of all cases (or at least all cases at risk), and microanalysis of fetal blood is used as a guide to the

obstetric management of labor once pathological changes in FHR are detected. The problem of false positives was alluded to in the previous section--the case where a low fetal pH during labor does not reflect a state of fetal hypoxia. The clinical condition of these infants at birth is so good (Apgar $\geq$ 7) that rapid extraction would not have been justified.

More detailed analysis of fetal pH along with maternal pH has been suggested as a means of obtaining a clearer clinical picture.

Roversi, for example, suggests four methods:[8]

1. Difference between fetal and material base deficit (F/M Δ BD)--comparison of the metabolic component of the acid-base balance.
2. Differences between maternal and fetal pH qu 40 (M/F Δ pH qu 40)--pH of the blood after equilibration of CO_2 at a P_{CO_2} of 40 mmHg.
3. Differences between the actual maternal and fetal pH (M/F actual Δ pH).
4. Materno-fetal difference in base deficit of extracellular fluid (M/F Δ BD Hb_5)--base deficit calculated on the basis of the amount of red cells distributed throughout the interstitial space, at an Hb concentration of 5 g/100 mℓ (BD Hb_5)

Work by Roversi, et al, indicates that the most meaningful of the various parameters so far suggested in M/F Δ BD Hb_5.

From our survey of recent papers it appears that an additional, continuous indicator of fetal acid-base balance is desirable. For example, in a study by Stalig of 4396 deliveries, FSB samples were obtained in 850 cases.[9] Fifteen infants were born with advanced or severe metabolic acidosis, although during labor fetal blood samples were normal. In a paper by Beard, Morris, and Clayton, it is concluded that the level of fetal pH does not necessarily reveal either the duration or the severity of the preceding intrauterine asphyxia.[10]

It is possible that a continuous indication P_{O_2} sensor or a continuous indicating P_{CO_2} sensor, or both, which attach to the scalp integral with the fetal

scalp ECG electrode, may provide the needed clinical indicators of fetal hypoxia. The use of intravascular sensors for this purpose seems inappropriate, however, for several reasons. The first of these is the size of the sensor(s). It is desirable to attach the sensor as early as possible, and the presenting surface may be very small. The second hurdle is the potential for trauma; viral and bacterial infections have been reported incidental to the use of spiral scalp electrodes. The third problem relates to sensor calibration vs. sterility requirements. Calibration prior to sterilization is usually not satisfactory, because potential offsets may be induced by chemical or heat sterilization, and calibration after sterilization is usually unsatisfactory because of the potential for contamination. It appears that these problems can be largely overcome through the use of transcutaneous sensors.

In this area, the work of A. and R. Huch is notable.[11] In this recent (June 1976) summarizing article, the extent to which this sensor has application is discussed. Not only is it valuable for fetal oxygen monitoring during delivery but it appears valuable in postpartum monitoring of infants--especially preterm newborns--and in the larger arena of anesthesia, postsurgical, and intensive care.

The functioning of a transcutaneous P_{O_2} electrode depends upon raising the P_{O_2} at the skin surface from its normal zero level to something approaching arterial blood P_{O_2}. The work of Huch indicates that a controlled temperature increase of the skin beneath the Clark-type O_2 sensor is effective. The electrode body is allowed to reach 45°C for adults and 44°C for prematures. This results in a 43° to 44°C skin temperature. The heat energy required to maintain this temperature is related to capillary blood flow--i.e., an indicator of relative perfusion in the area. The transcutaneous P_{O_2} (TcP_{O_2}) electrode as fabricated by Huch consists of a ring-shaped silver anode heated by a coil to provide local hyperemia. Within the anode are three thin platinum cathodes, only 15 μm in diameter. The working face is covered by a double membrane of Teflon and cellophane. A potassium chloride electrolyte is used.

Especially good correlation between $TcPO_2$ and arterial PO_2 for neonates has been observed by Huch--r = .97. For Ob-Gyn and surgical patients, r = .92. Time lags of no more than 10 seconds have been achieved with infants. At this time accurate PO_2 readings are obtained from the fetal scalp as soon as the cervix is dilated at least 4 cm.

In another recent paper by Huch, et al,[12] thirty long-term continuous $TcPO_2$ recordings were made and compared with 132 arterial PO_2 determinations. A linear relationship between arterial PO_2 and $TcPO_2$ (r = .94) was observed. The quality of the correlation was not influenced negatively by the length of the $TcPO_2$ recordings, nor was any skin damage observed.

Others have fabricated and used transcutaneous PO_2 electrodes. Swanstrom has used this method for monitoring the newborn infant with acceptable results.[13] He expressed concern about the possibility of a vasoconstriction confusing the readings, although this problem did not occur during this study.

Scacci, et al,[14] have used the transcutaneous oxygen electrode and feel that it is a satisfactory indicator of changes in arterial PO_2 in the fetus with good peripheral circulation. They found that it is possible to estimate PaO_2 over intervals of 24 hours with an average error of 15 mmHg.

Attractive as a continuous measuring PO_2 electrode is for assessing fetal hypoxia status, the final determination of the extent of fetal acid-base status is made by pH or PCO_2 analysis of fetal capillary blood. The work with transcutaneous PO_2 electrodes has stimulated work with transcutaneous PCO_2 electrodes of similar geometry. The work by Beran, Huxtable, and Sperling demonstrates a departure from the common PCO_2 electrode.[15] Traditionally, membrane PCO_2 electrodes have been constructed using the principle of Stow--a glass pH electrode and reference electrode are bathed in bicarbonate buffer and covered with a membrane diffusible to CO_2 molecules. This carbon dioxide reacts with the buffer which dissociates to H^+ and HCO_3^-. The resultant pH change is sensed by the pH electrode and expressed as a PCO_2 change. Beran has fabricated and tested an antimony-antimony oxide (Sb-SBOx) electrode against a silver-silver

chloride (Ag-AgCl) reference electrode. The resulting sensor is similar to the Huch transcutaneous P_{O_2} electrode--having a heater with thermistor for thermal control, 3 Sb-SBOx electrodes within a central structure, and Ag-AgCl reference. A 13-μm Teflon membrane is used with the standard CO_2 electrolyte (water $NaHCO_3$, KCL). *In vivo* studies have been performed on rabbits and human volunteers. Response time of the sensor appears to be slightly less than 3 minutes (95%). Good results were obtained between TcP_{CO_2} and arterial P_{CO_2} in the rabbit. The equation of the line TcP_{CO_2} = arterial P_{CO_2} x 1.029 - 4.39. The standard deviation of the points along the line was 4.140.

pH measurements would also be of value in the assessment of acid-base status.

Although a continuous indication of fetal scalp blood pH would complete the standard acid-base measurement, the practicality of constructing a pH electrode of fragile glass is questionable. Small percutaneous pH sensors for muscle surface measurements have been fabricated and are commercially available. A dual-function pH and P_{CO_2} *in vivo* sensor has also been reported on by Coon, et al.[16] This device is intended for intravascular application.

A paper by Stam, et al,[17] describes a subcutaneous pH sensor for fetal scalp application. The glass pH sensor has spiral springs for insertion into the fetal scalp. Good correlation between subcutaneous pH mean value and capillary blood mean value produced a correlation coefficient of $r = .965$ ($P<0.001$). Because pH measurements are of necessity invasive, however, there are problems associated with calibration and maintenance of sterility.

In theory, the new field-effect transistors that are chemical or ion sensitive could measure pH or H^+ ion concentration. Based on limited experience with these sensors, it appears that considerable research is required before they are directly applicable to the fetal monitoring arena.[18,19]

When manufacturability, ease of calibration (calibration must result in a sterile sensor ready for application), and ruggedness are considered, it appears that the membrane covered transcutaneous P_{O_2} and P_{CO_2} sensors have some considerable advantages. The fetal scalp ECG electrode appears to be an easy addition to the P_{O_2}-P_{CO_2} sensor assembly. Possibly a capacitively-coupled

electrode adjacent to the membrane covered unit would provide the necessary simultaneous ECG signals with minimum cervical dilation.

IV. CONCLUSIONS AND RECOMMENDATIONS

If the desired configuration of an intrapartum monitoring system is a single sensor capable of measuring multiple determinations of fetal health, we must conclude that a satisfactory sensor is not currently available. Recent reports and research in progress indicate that the elements of such a sensor are well advanced in their development states. The obvious next step is to create a multiparametric sensor capable of making simultaneous measurements from a single point of attachment.

V. A COMBINED FETAL MONITORING PROBE

A combination fetal monitoring electrode could make a significant contribution to the clinical management of the fetus and neonate. In order for such an electrode to satisfy clinical requirements, a number of design objectives must be initially identified and carefully adhered to throughout the development phase.

The following list of design objectives is provided for consideration:

1. The probe must be rugged and durable--or it must be inexpensive and disposed of after a single use.
2. It must be carefully integrated and sufficiently small so monitoring can begin very early in labor--preferably when the cervix dilation is no more than 2 cm.
3. Calibration prior to use must be quite straightforward. The probe could be automatically calibrated for P_{O_2} and P_{CO_2} by some form of closed loop procedure--for example, the probe might be immersed in a tonometered mixture or exposed to a sterile gas mixture with continuous and automatic adjustment of the O_2 and CO_2 amplifiers.

4. Sterility must be maintained during calibration.

5. The entire probe assembly must be totally isolated from the readout/display. Optical isolators now effectively isolate into the kilovolt region and may offer a solution to this problem.

6. If the probe is reused, minimum routine maintenance must be adequate to maintain the probe for many months--in other words, there can be no changing of membrane, adding to electrolyte, etc. Beckman's experience with pregelled P_{O_2} sensors proves without a doubt the wisdom of this approach in clinical medicine.

A desirable approach for the development of the probe would be for both blood gas sensors to share a common cathode, electrolyte, and membrane. Since no research to our knowledge has been done on a combined Clark P_{O_2} and SbSBOx P_{CO_2} electrode, this should be further explored. It has been established, however, that the standard Clark electrode and Stow-Severinghaus electrode can operate with a common electrolyte.

Since FHR is vital to the fetal monitoring, a combined electrode should have built-in provision for detecting the fetal ECG integral.

The spiral ECG electrode has become popular in recent years, and currently offers the highest quality ECG signal with the safest attachment concept. Huch has fabricated a transcutaneous P_{O_2} electrode with a silver ring ECG electrode. The entire unit is held to the scalp with vacuum. The vacuum approach is appealing since it causes little tissue damage. It would be desirable to avoid puncturing the fetal scalp for two reasons:

1. Less danger of infection.
2. Fluid exudation would not interfere with the operation of the membrane sensors.

Reliability of any fetal ECG electrode not producing a puncture is open to question. However, a combination probe must not under any circumstances degrade the quality of the FHR traces--the most reliable and dependable aspect of present-day fetal monitoring.

We feel that a combined sensor assembly would offer the most significant advance for the clinician. The active fetal ECG electrode and its reference electrode would be integrated into the sensor body. A dual transcutaneous P_{O_2} and P_{CO_2} electrode with common elements would complete the sensor assembly. The significant technical objective would be to design and fabricate a functioning P_{O_2}-P_{CO_2} unit with common gel electrolyte, common membrane materials, and shared Ag-AgCl reference or anode. A single cathode structure is proposed with gold or platinum for the polarographic O_2 sensor, and either Sb-SBOx material or glass bulb for the CO_2 sensor.

The choice of antimony oxide vs pH glass for P_{CO_2} will depend on investigations presently under way by Huxtable and Beran (personal communication). Vacuum attachment concepts should be initially explored--an Ag-AgCl surface should provide the high quality fetal ECG signal so necessary for fetal artifact-free FHR patterns.

A sketch of the proposed sensor is shown in Figure 1.

Figure 1, which includes details of the tissue contacting portion of the proposed sensor only, indicates the following key elements:

1. Fetal tissue temperature control section--including thermistor and heating element.
2. An Ag-AgCl active fetal ECG electrode--with reference electrode depicted.
3. A gelled electrolyte with large reservoir for maximum sensor life at elevated operating temperature (42° to 44°C).
4. A temperature-indicating thermistor for compensation of membrane temperature coefficient.
5. A common Ag-AgCl anode structure within the electrolyte.
6. Antimony-Antimony oxide elements for P_{CO_2} measurements.
7. A gold or platinum cathode for polarograpic O_2 sensors.

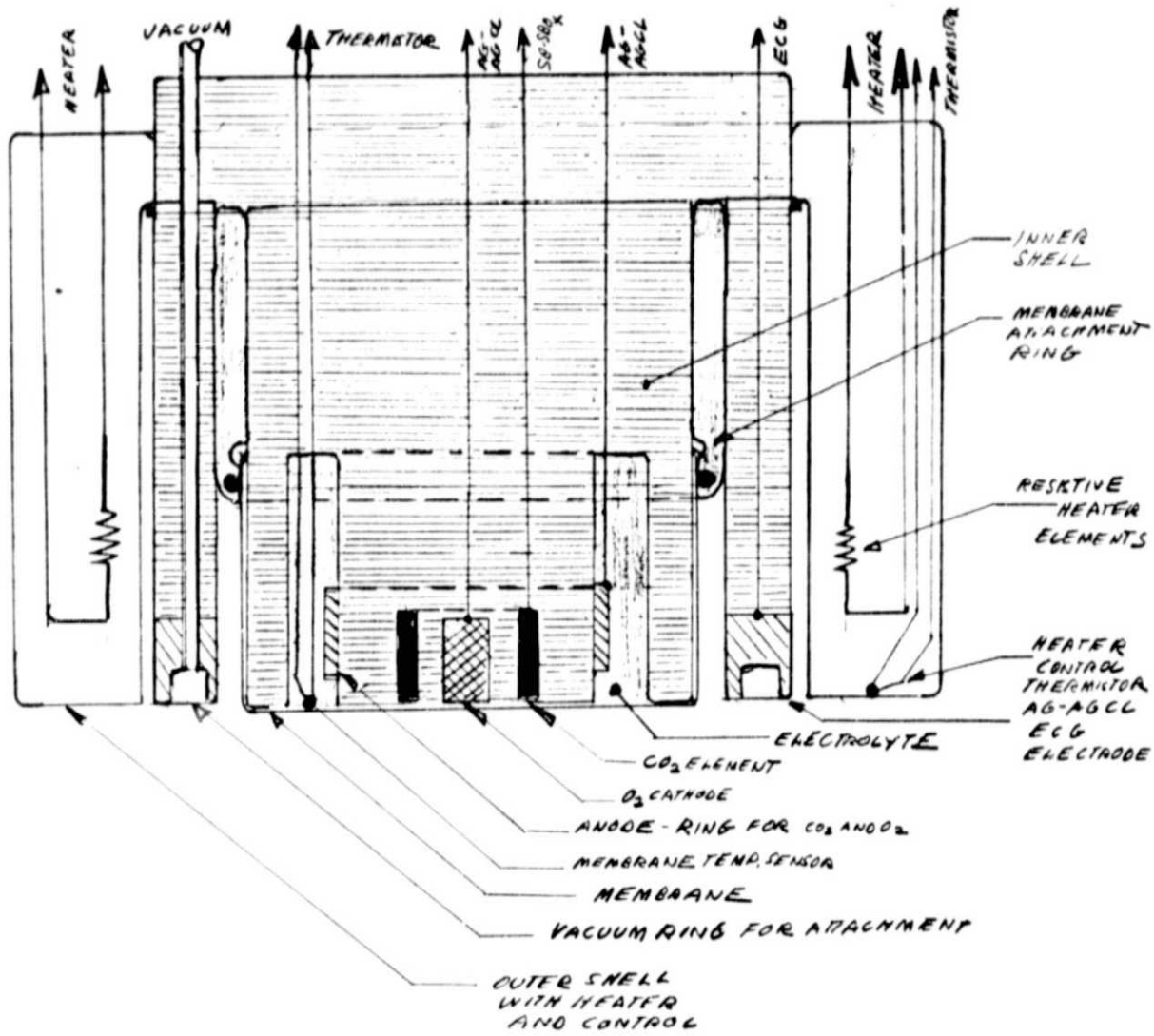

Figure 1. Proposed Combined Fetal ECG, P_{O_2} and P_{CO_2} Sensor

Figure 2 is a block diagram of the readout-control circuit which would be suitable for commercial use. To meet the requirements of the Food & Drug Administration (FDA) for this class of instrument, isolated power and recorder drive circuits are required (Section VI).

The proposed fetal monitoring system would include 4 channels of output. A final commercial package would most likely integrate the 4 channels with the readout and control circuits to provide a simple and useful package. A microprocessor for control logic would contribute to the clinical usability of the final commercial product.

We suggest that initial efforts be directed towards designing, fabricating, and evaluating the patient-contacting elements shown in Figure 2. To maximize this effort, as many as possible of the blocks depicted in the condition circuits section should be purchased off the shelf. For example, blocks 5 and 6 essentially exist as commercial fetal monitoring units, available for $5000 to $8000. Block 4, the Membrane Temperature Amplifier, could be obtained off the shelf. Block 2, the Tissue Temperature Controller, is available as a standard product and could be used directly with minor modifications. Block 3--the P_{O_2} and P_{CO_2} amplifiers--must be developed integral with the P_{O_2} and P_{CO_2} sensors to achieve the proper impedance, biasing, and control. Standard digital panel meters could be used in the initial effort.

Although the combined FECG/P_{O_2}/P_{CO_2} sensor must be evaluated and proved in an obstetrical environment, we believe initial evaluation should begin on animals and adult humans. The system, as described, should go through a rigorous evaluation using animals and adult humans before being applied to the fetus. The data obtained in such a manner would probably be required to meet FDA guidelines for a product of this nature.

VI. REGULATIONS AFFECTING DEVELOPMENT

The type of instrumentation discussed in this report is expected to be subject to FDA Medical Devices Amendments of 1976. The Amendments established three

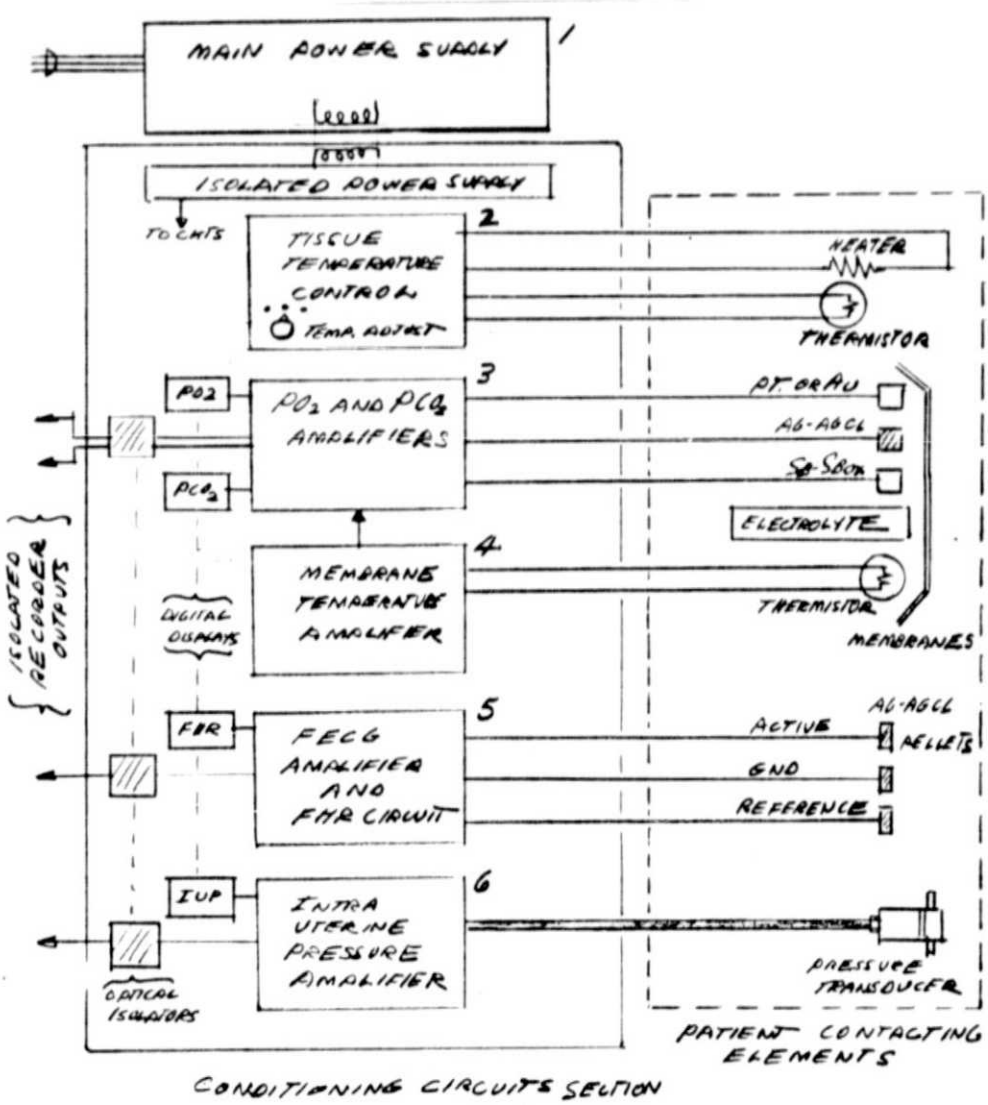

Figure 2. Fetal Monitoring System with Combination FECG, P_{O_2} and P_{CO_2} Sensor

levels of regulatory control of medical devices: Class I (General Control); Class II (Performance Standards): and Class III (Premarket Approval). Classification of medical devices under the Amendments has not been completed, but based on classification activities to date, it would appear that a fetal monitoring device would be at least Class II and could possibly be Class III. Until device classification is completed by the FDA, all new devices (not on the market prior to May 28, 1976) that are life-supporting or life-sustaining are presumed to be Class III until a less rigorous classification can be justified.

The Class II level of regulatory control requires a device to be manufactured in accordance with a federally-established performance standard. The performance standard established by the FDA, where necessary to provide reasonable assurance of safe and effective performance of device, will include:

1. Provisions for the detailed performance requirements of the device and its compatibility with power systems and connections;
2. Provisions for the testing of the device;
3. Provisions for the measurement of the performance characteristics of the device;
4. Provisions that the results of the device testing show that the device is in conformance with the standard for which the test was required; and
5. Provisions for the labeling for the device.

The performance standard that will eventually evolve will normally be effective one year after its publication in the Federal Register unless the FDA determines that an earlier effective date is necessary for the protection of the public health and safety. Until performance standards are published for devices in Class II, unless otherwise specified, all such devices will be subject to the more general controls of Class I which consist mainly of good manufacturing practices. The Class III level of regulatory control requires FDA review and approval of data on safety and effectiveness of a medical device prior to

placing the device on the market. Detailed scientific studies will be required from which the FDA can arrive at conclusions regarding device safety and effectiveness.

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